the column. The solvent was removed from the combined solutions and the residue was distilled under 0.001 mm. as before. It weighed 0.42 g., had $n^{25}D$ 1.5059, and gave the U. V. spectrum shown in Fig. 2.

Anal. Calcd. for $C_{29}H_{49}OBr$: C, 70.56; H, 10.00. Found: C, 70.54; H, 9.83.

The bromocoumaran VIc (0.33 g.) and cyclohexyl bromide (0.22 g.) in ether (10 cc.) was stirred with magnesium (0.163 g.) while the magnesium was reacting with ethyl bromide (0.21 g.) in ether (10 cc.). The procedure and processing of the reaction mixture were carried out as described above in the preparation of Ib. The crude product was distilled from a pot-still at 170–200° (bath temperature) under 0.001 mm.; the orange distillate weighed 0.25 g. It gave a positive Folin–Denis test, and contained a trace of halogen. A solution of the oil in petroleum ether (30 cc.) was passed through a column of alumina (Brockmann); the column was washed with additional petroleum ether and the combined organic solutions were evaporated. The residue was distilled as before. The distillate (about 0.1 g.) gave an absorption spectrum in the U. V. which in no way resembled those of Ia and Ib. The column of alumina was eluted with ethanol, but very little material was present in the eluate and this material, likewise, was not a hydroxycoumaran.

Summary

1. Three ketones—methyl ethyl ketone, methyl *n*-amyl ketone, and "phytol" ketone—have been condensed with 4,6,7-trimethylcoumaran-3-one (III) to give the 2-alkylidene coumarones.

2. The alkylidene coumarones from the last two ketones were reduced to the coumarans, and the latter were brominated in the 5-position.

3. The 5-bromocoumaran thus obtained from methyl *n*-amyl ketone was converted to a Grignard reagent, and the latter was oxidized, producing the 5-hydroxycoumaran. Conversion of the 5-bromocoumaran derived from phytol ketone into the analogous 5-hydroxycoumaran was not achieved.

4. Curves are given showing the absorption spectra in the ultraviolet of several of the intermediates and final products.

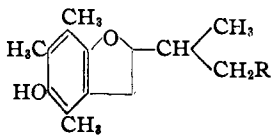
MINNEAPOLIS 14, MINNESOTA RECEIVED APRIL 2, 1948

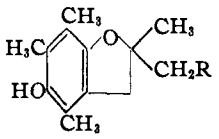
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Vitamin E. XLVII.[1] The Coumaran Isomer of α-Tocopherol

BY LEE IRVIN SMITH AND GERALD A. BOYACK[2]

Early in the history of the work upon the structure and synthesis of α-tocopherol, there was some discussion as to whether the vitamin was best represented as a coumaran, I, or as the isomeric chroman, II.[3]





I, R = $C_{16}H_{31}$ = 3,7,11-trimethyldodecyl. II, R = $C_{16}H_{31}$

Although the structure was definitely settled in favor of II,[4] a synthesis of the isomeric coumaran I would be of some interest, in view of the vitamin E activity of many compounds related to II. This paper describes a successful synthesis of I and one of its homologs X (R = *n*-$C_{13}H_{27}$). The coumaran I was obtained as a yellow oil and, although it showed vitamin E activity, the activity was only about 5% of that of α-tocopherol.

(1) Smith and Boyack, XLVI, THIS JOURNAL, **70**, 2687 (1948).

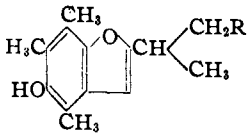
(2) Abstracted from a thesis by Gerald A. Boyack presented to the Graduate Faculty of the University of Minnesota, in partial fulfilment of the requirements for the Ph.D. degree, September, 1947.

(3) (a) Bergel, Todd and Work, *J. Chem. Soc.*, 253 (1938); (b) Karrer, Salomon and Fritzsche, *Helv. Chim. Acta*, **21**, 309 (1938); (c) Karrer, Fritzsche, Ringier and Salomon, *ibid.*, **21**, 520 (1938); (d) Fernholz, THIS JOURNAL, **60**, 700 (1938); (e) John, *Z. physiol. Chem.*, **252**, 222 (1938).

(4) (a) John, Dietzel, Günther and Emte, *Naturwiss.*, **26**, 366 (1938); (b) Karrer, Escher, Fritsche, Keller, Ringier and Salomon, *Helv. Chim. Acta*, **21**, 939 (1938); (c) Smith, Ungnade and Prichard, *Science*, **88**, 37 (1938); (d) Tishler and Wendler, THIS JOURNAL, **63**, 1532 (1941); (e) Smith, Ruoff and Wawzonek, *J. Org. Chem.*, **6**, 236 (1941); (f) Smith and King, THIS JOURNAL, **65**, 441 (1943).

The synthetic route to I involved the sequence of compounds III to VII (R as in formula I): the coumaron VII was then catalytically reduced to I.

III, $RCH_2C(CH_3)=CHCH_2OH$
IV, $RCH_2CH(CH_3)CH_2CH_2OH$
V, $RCH_2CH(CH_3)CH=CH_2$
VI, $RCH_2CH(CH_3)R'$
VIa, R′ = COOH
VIb, R′ = COCl
VIc, R′ = $COCH_3$
VId, R′ = $COCH_2COCH_3$



VII

Phytol (III) was catalytically reduced to dihydrophytol (IV) and the latter was converted to the stearate. When the crude stearate was pyrolyzed, phytene-1 (V) resulted. Although phytene-1 had been reported twice previously[5] no proof that the double bond is terminal has ever been given. The phytene-1 prepared in the present work had the proper iodine number and its reaction with perbenzoic acid was very slow—much slower than the rate with which oleic acid reacts, and slower even than the reaction of undecylene-1, indicating in this phytene the absence of a disubstituted double bond. Finally, ozonolysis of phytene-1 followed by oxidative decomposition of the ozonide, led to apophytoic acid VIa. The acid was converted into the acid chloride VIb and from this the methyl ketone VIc was prepared by action of dimethylcadmium.[6] A solid derivative of the methyl ketone VIc was not obtained; both the

(5) (a) Willstätter and Hocheder, *Ann.*, **354**, 255 (1907); (b) Willstätter, Mayer and Huni, *ibid.*, **378**, 91 (1911); (c) Karrer, Helfenstein and Widmer, *Helv. Chim. Acta*, **11**, 1201 (1928).

(6) Cason and Prout, THIS JOURNAL, **66**, 46 (1944).

semicarbazone and the 3,5-dinitrophenylhydrazone were liquids.

When the methyl ketone VIc reacted with ethyl acetate in the presence of sodamide, the diketone VId resulted. This gave a red color with ferric chloride, but no solid derivative was obtained; although VId formed a copper derivative, this was a liquid. Condensation between methyl apophytate and acetone in the presence of sodamide, which likewise would lead to VId, was unsuccessful—the chief product was apophytoic acid.

When a mixture of the diketone VId, trimethylquinone, and sodium ethoxide was allowed to stand for a week, the coumaron VII was obtained as a dark oil. The coumaron was characterized by analysis and by the U.V. absorption spectrum (Fig. 1), which exhibited maxima at the same wave lengths as shown by the spectrum of 2,4,6,7-tetramethyl-5-hydroxycoumaron.[7] The coumaron VII was reduced by action of hydrogen at 68° in the presence of a palladium catalyst; the product was the coumaran I, characterized by analysis, by conversion to a solid allophanate melting at 176–180° (m. p. of the allophanate of α-tocopherol, 158–160°)[8] and by the U. V. absorption spectrum (Fig. 1) which was quite similar to that of the simple isopropyl homolog (I, R = H).[1] The absorption spectrum of I was similar to that of α-tocopherol.[9] Curiously enough, the absorption spectrum of the allophanate of I was somewhat different from that of α-tocopheryl allophanate[10] but was almost identical with that of β-tocopheryl allophanate.[3a] The coumaran I was assayed biologically for Vitamin E activity[11] and the results showed that I possessed about 5% of the activity of *dl*-α-tocopherol. This is somewhat surprising, in view of the comparable activity of many compounds much less closely related structurally to α-tocopherol than I is, and in view of the fact that α-tocopherylamine is about as active as is α-tocopherol itself. It thus appears that the size of the ring—5 or 6—is a critical factor for vitamin E activity.

Before the experiments described above were undertaken, many model experiments were carried out. The route to the coumarans was based upon the work of Smith and Kaiser,[12] who added the enolate of acetylisobutyrylmethane to trimethylquinone and converted the resulting phenylated diketone, by action of hydrochloric acid, into a mixture of two 2-alkyl-4,6,7-trimethyl-5-hydroxy-

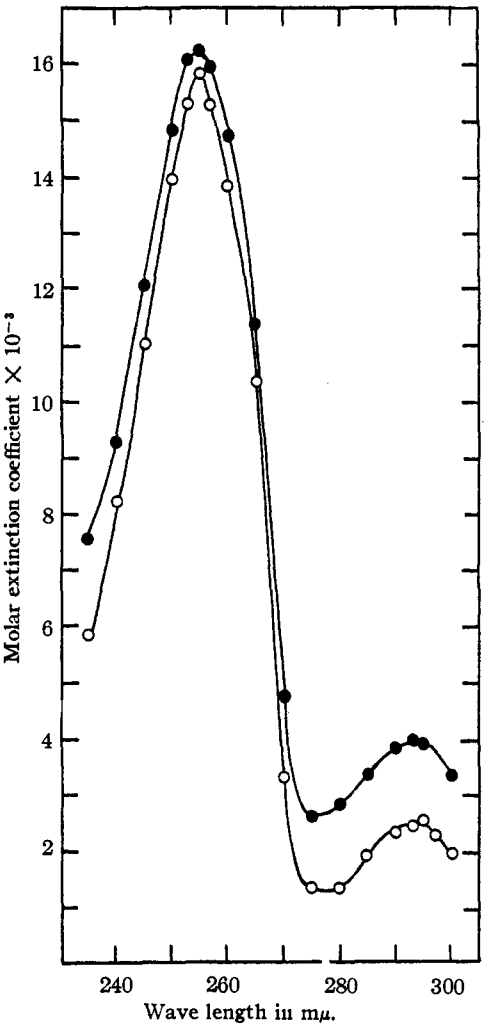


Fig. 1.—Absorption spectra: O, 2-(6′,10′,14′-trimethyl-2′-pentadecyl)-4,6,7-trimethyl-5-hydroxycoumaron; ●, 2-tridecyl-4,6,7-trimethyl-5-hydroxycoumaran: solvent, 95% ethanol.

coumarons—the 2-methyl and the 2-isopropyl. This situation always arises when the starting diketone is unsymmetrical and the two alkyl groups have molecular weights close together; moreover, the resulting coumarons are separated only with great difficulty. Because of these facts, Smith and King[4f] in their synthesis of 2-isopropyl-4,6,7-trimethyl-5-hydroxycoumaran (I, R = H) used the symmetrical diisobutyrylmethane as the starting diketone and so obtained only one coumaron. However, application of King's synthesis to the preparation of I offered formidable difficulties, for preparation of the intermediates necessary for conversion to the proper diketone involved many steps from the most accessible material, phytol. All of these intermediates, as well as the final product of the Claisen condensation, are liquids with very high boiling points, extremely difficult to purify. Consequently, if the approach to the synthesis of I could be made via Kaiser's method, the

(7) Webb, Smith, Bastedo, Ungnade, Prichard, Hoehn, Wawzonek, Opie and Austin, *J. Org. Chem.*, **4**, 389 (1939).

(8) Evans, Emerson and Emerson, *J. Biol. Chem.*, **113**, 319 (1936).

(9) Ref. 7; also Emerson, Emerson, Mohammed and Evans, *J. Biol. Chem.*, **122**, 99 (1937).

(10) John, *Naturwiss.*, **26**, 449 (1938).

(11) These assays were carried out by Dr. Paul D. Boyer and Mr. E. Liebe, of the Division of Agricultural Biochemistry, University of Minnesota, to whom the authors are greatly indebted. The method was that of K. E. Mason (*Biol. Symp.*, **12**, 1947). The minimum fertility dose (100% "litter efficiency") of I was between 15.0 and 17.5 mg.: in concurrent assays, the minimum fertility dose of *dl*-α-tocopherol was 0.75 mg.

(12) Smith and Kaiser, THIS JOURNAL, **62**, 133 (1940).

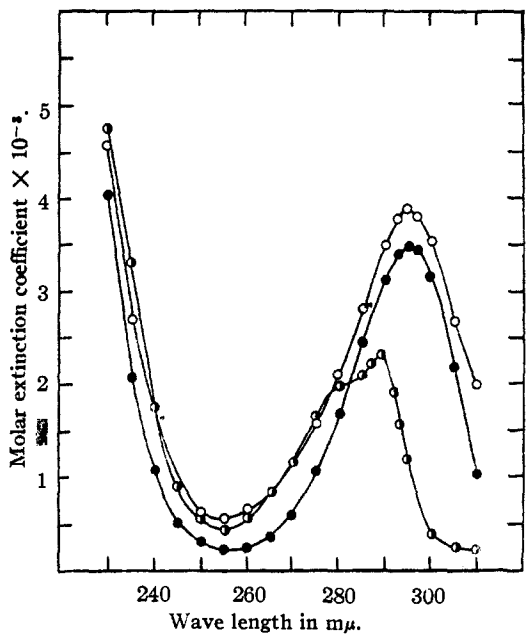
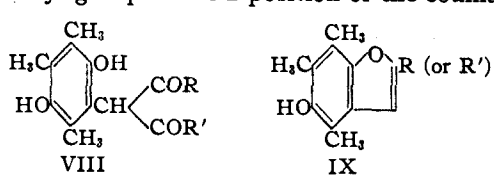


Fig. 2.—Absorption spectra: O, 2-(6',10',14'-trimethyl-2'-pentadecyl)-4,6,7-trimethyl-5-hydroxycoumaran: ●, 2-tridecyl-4,6,7-trimethyl-5-hydroxycoumaran: ◑, 2-(6',10',14' - trimethyl - 2' - pentadecyl) - 4,6,7 - trimethyl-5-hydroxycoumaran allophanate: solvent, 95% ethanol.

synthetic problems would be much simplified. Since the phenylated diketone VIII is an intermediate, the point of cleavage of this diketone during the ring closure determines the nature of the alkyl group in the 2-position of the coumaron



IX. Kutz and Adkins[13] have shown that, when an acetylacylmethane CH_3COCH_2COR, is hydrolyzed by action of alkali, cleavage on the acetyl side of the molecule is promoted by increasing length and complexity of the group R. Therefore it appeared that if the group R in the diketone were large, the synthesis would lead to a mixture of coumarons in which the simpler 2-methylcoumaron would constitute but a minor proportion. If so, separation of the two coumarons should not offer much difficulty because the simple 2-methylcoumaron is quite volatile with steam. These expectations were fully justified; when myristoylacetylmethane was added to trimethylquinone and the resulting phenylated diketone was converted into coumarons, about three moles of IX, R = n-$C_{13}H_{27}$, were formed for every mole of IX, R = CH_3. The two coumarons were readily separated for IX, R = CH_3, is quite volatile with steam whereas IX, R = n-$C_{13}H_{27}$, is only slightly so. In the synthesis of I, none of the simple 2-methylcoumaron was obtained; ring closure led entirely to VII (R as in I).

The route to IX, R = n-$C_{13}H_{27}$, involved the same sequence of reactions that was used for synthesis of I. Myristoyl chloride was converted into pentadecanone-2 by reaction with dimethylcadmium.[6] In this reaction, a considerable amount of dimyristoylmethane was also formed. Pentadecanone-2 was converted into heptadecandione-2,4 by condensation with ethyl acetate in the presence of sodamide, in yields slightly better than those obtained when metallic sodium was used.[14] The diketone existed 100% in the enolic form, a finding in accord with the results of Weygand and Baumgartel[15] that the amount of enolic form at equilibrium in an acetylacylmethane increases with the length of the acyl group. Only poor yields of the diketone, accompanied by much myristic acid, were obtained when methyl myristate was condensed with acetone in the presence of sodium hydride according to the procedure of Hansley,[16] who stated that the diketone was produced in good yields. Condensation of the diketone with trimethyl quinone in the presence of sodium ethoxide, according to the procedure of King,[4f] offered no difficulty although a considerable amount of the diketone was recovered unchanged. Conversion of the phenylated diketone VIII to coumarons was effected by action of boiling dilute sodium hydroxide, although during the reaction air had to be carefully excluded. The phenylated diketone VIII was unaffected by hot hydrochloric acid, in contradistinction to the lower homologs, which are converted to coumarons by this reagent.[12] The coumaron IX (R = n-$C_{13}H_{27}$) was reduced to the corresponding coumaron (X, R = n-$C_{13}H_{27}$) by the action of hydrogen in the presence of a palladium catalyst.[17] Raney nickel catalyst under conditions of high temperature and pressure was without effect upon IX; this catalyst has been found effective for reduction of the lower homologs of IX.[18]

The melting points of the coumaran IX (R = n-$C_{13}H_{27}$) and the corresponding coumaran X are close together and a mixture of the two compounds does not show a depressed melting point. Nor does elementary analysis serve to distinguish between them. However, the absorption spectra in the ultraviolet are quite different for the two

(13) Kutz and Adkins, THIS JOURNAL, 52, 4036 (1930).

(14) Morgan and Holmes, *J. Chem. Soc.*, 2891 (1925).

(15) Weygand and Baumgartel, *Ber.*, 62, 574 (1929).

(16) Hansley, U. S. Patent 2,218,026 (1940).

(17) Bergel, Jacob, Todd and Work, *J. Chem. Soc.*, 1375 (1938).

(18) Ref. 4f; also Smith, Ungnade, Hoehn and Wawzonek, *J. Org. Chem.*, 4, 305 (1939).

compounds; the curves are given in Figs. 1 and 2. The curve for this coumaran is very similar to those reported for other known 2-alkylcoumarans.[7]

Experimental Part[19]

Dihydrophytol IV.—Phytol (III, 200 g.)[20] was subjected to the action of hydrogen at 175° for one hour in the presence of Raney nickel catalyst, and under an initial hydrogen pressure of 2800 lb. The catalyst was removed and the product was distilled. The fraction boiling at 164–166° (0.01 mm.) did not decolorize bromine in carbon tetrachloride; it weighed 176 g. (85%) and had $n^{20}D$ 1.4520.[21]

Phytene-1 (V).—Dihydrophytol (166 g.) was heated at 125° (bath temperature) with stearoyl chloride (180 g.) for three hours. The cooled mixture was washed twice with double its volume of cold (10°) methanol. The crude liquid ester (329 g., free from chlorine) was pyrolyzed by dropping it slowly into a distilling flask immersed in a bath at 420°. The solid distillate (318 g.) was heated at 160° (bath temperature) under 0.01 mm. until there was no further distillate (phytene-1). The residue was washed with cold methanol to remove stearic acid, and was then distilled from a pot still at 340–380°. The olefin in the distillate was removed at 160° under 0.01 mm. as before, and the two olefin fractions (130 g.) were combined and allowed to stand over sodium for four days, with removal of the gelatinous material each day. The material was then distilled; the fraction boiling at 120–127° (0.01 mm.) weighed 86 g. (55%) and had $n^{25}D$ 1.4430.

Anal. Calcd. for $C_{20}H_{40}$: C, 85.63; H, 14.37; iodine number, 90.8. Found: C, 85.47; H, 14.09; iodine number, 91.4.[22] In three hours at 25° phytene-1 reacted with perbenzoic acid to the extent of 34.5%; under the same conditions, undecylene-1 and oleic acid gave the respective values of 44% at 100%.[23]

Apophytoic Acid (VIa).—Phytene-1 (V, 28 g.) in petroleum ether (200 cc., b. p. 28–38°, washed with sulfuric acid and dried over sodium) was ozonized at −50 to −40° by passing through the solution a stream of ozone–oxygen (0.4% O_3)[24] until approximately a third of the ozone was coming through unabsorbed. The solution was added to a stirred suspension of silver oxide (from silver nitrate, 46 g. and 1 *N* sodium hydroxide, 250 cc.) in aqueous sodium hydroxide (220 cc., 5%) at 95°. Petroleum ether distilled rapidly, and after all this solvent was removed, the mixture was stirred and heated on the steam-bath for eight hours. Chloroform (100 cc.) was added to the cooled and stirred suspension, which was then slowly acidified with nitric acid (80 cc.). The chloroform layer was removed, washed with water, dried over sodium sulfate, and the solvent was removed by distillation. The residues (28.3, 28.6 and 27.5 g.) from three such runs were combined and distilled from a Clarke flask under 0.01 mm. A low boiling fraction (6 g., odor of butyric acid) and an intermediate fraction (16 g., neutral), were followed at 175–185° by a fraction of apophytoic acid (51 g., 57%) having $n^{25}D$ 1.4489.

Anal. Calcd. for $C_{19}H_{38}O_2$: C, 76.45; H, 12.83; neut. equiv., 298. Found: C, 76.57; H, 12.80; neut. equiv., 297.

The methyl ester (49.8 g., 98%) prepared from the acid (48 g.) by action of diazomethane (from 25 g., nitrosomethylurea) in ether (100 cc.) boiled at 125–133° (0.01 mm.) and formed a neutral liquid.

Anal. Calcd. for $C_{20}H_{40}O_2$: C, 76.86; H, 12.90. Found: C, 76.97; H, 12.83.

Apophytoyl Chloride (VIb).—The acid VIa (27 g.) was refluxed in thionyl chloride (53.5 g.) for one hour. Excess thionyl chloride was removed at 120° (bath temperature) under 20 mm., and the residual acid chloride was distilled under 0.01 mm. It boiled at 165–170° and weighed 23.2 g. (81%).

Anal. Calcd. for $C_{19}H_{37}OCl$: C, 72.01; H, 11.77; Cl, 11.2. Found: C, 72.86; H, 12.30; Cl (Volhard), 10.7.

3,7,11,15-Tetramethylhexadecanone-2 (VIc).—A Grignard reagent was prepared by passing a current of methyl bromide into a stirred suspension of magnesium (3.58 g.) in ether (200 cc.) until the metal dissolved completely. To this solution, cadmium chloride (14.8 g., dried at 100° and powdered) was added all at once and the mixture was stirred and refluxed for ten minutes. Ether was removed by distillation until a mush of solid remained, then dry benzene (100 cc., thiophene-free) was added and distillation was continued until the temperature of the vapors reached 70°. More benzene (100 cc.) was added, the mixture was heated to the boiling point, and apophytoyl chloride (VIb, 23 g.) was added to the refluxing suspension as rapidly as the exothermic reaction would permit. The mixture was stirred and refluxed for thirty minutes longer, and was then poured over ice and acidified with hydrochloric acid until most of the solid dissolved. The organic layer was removed, and the aqueous layer was extracted with benzene. The combined organic layers were washed with water until the washings were neutral. The solution was dried over sodium sulfate and the solvent was removed by a flash distillation at 150°. The residue, distilled under 0.01 mm. gave a fraction boiling at 180–185° (11.1 g.) which had $n^{25}D$ 1.4453.

Anal. Calcd. for $C_{20}H_{40}O$: C, 81.01; H, 13.60. Found: C, 80.87; H, 13.71.

Additional ketone (1.3 g.) slightly less pure, was obtained by heating the residue from the above distillation in a pot still under 0.001 mm. at 130° (bath temperature). The total yield of ketone was 12.4 g. (58%). The residue remaining after removal of all the ketone, when distilled from a pot still at 210° (bath temperature) under 0.001 mm. gave a yellow oil (3 g.) having $n^{25}D$ 1.4650. It gave a red color with ferric chloride. This was probably a mixture of the 1,3-diketone $RCH_2CH(CH_3)COCH_2$-$COCH(CH_3)CH_2R$ and the aldol product of the ketone, $RCH_2C(CH_3)=CHCOCH(CH_3)CH_2R$.

Anal. Calcd. for $C_{39}H_{76}O_2$ (diketone): C, 81.87; H, 13.28. Calcd. for $C_{40}H_{78}O$ (aldol): C, 83.56; H, 13.68. Found: C, 82.83; H, 13.36.

The semicarbazone of VIc, distilled from a pot still at 145° (bath temperature) under 0.001 mm., was a viscous oil having $n^{25}D$ 1.4713 and which could not be induced to crystallize. Likewise, the 2,4-dinitrophenylhydrazone of VIc was a viscous red oil, insoluble in ethanol (VIc was quite soluble in ethanol).

5,9,13,17-Tetramethyloctadecandione-2,4 (VId).—Small pieces of sodium were added to liquid ammonia (100 cc.) until the blue color was permanent, whereupon a small crystal of ferric chloride was added and air was drawn through the solution until the blue color disappeared. Then sodium (3.42 g.) was added and the mixture was stirred until the blue solution became a gray suspension. The ammonia was allowed to evaporate, being replaced by dry ether so that the volume remained constant. The ketone VIc (11 g.) in dry ether (30 cc.) was added and the mixture was refluxed for twenty minutes, then dry ethyl acetate (32.2 g.) was added slowly (ten minutes). The mixture first became very viscous, even though more ether (50 cc.) was added, but soon became thin enough to stir. It was stirred for seven hours at room temperature and then poured over ice and acidified (congo red) with hydrochloric acid. The organic layer was removed, combined with an ether extract of the aqueous layer, and dried over sodium

(19) Microanalyses by R. Amidon, Jay S. Buckley and S. Sundet.

(20) The authors are greatly indebted to Dr. R. T. Major, of Merck and Co., Inc., for a generous supply of phytol.

(21) (a) Kuhn and Sugmoine, *Helv. Chim. Acta*, **12**, 916 (1929), report 1.4538; (b) Willstätter, *et al.*, ref. 5b, report 1.45213.

(22) Hickinbottom, "Reactions of Organic Compounds," Longmans, Green & Co., New York, N. Y., 1936, p. 212.

(23) Determinations by Mr. Tom Lee of the Division of Analytical Chemistry for which the authors are greatly indebted.

(24) The capacity of the transformer available; presumably higher concentrations would be equally effective.

sulfate. The solvent was removed and the residue, when distilled under 0.01 mm. gave a distillate (7.3 g., 58%) boiling at 150–153° and having $n^{25}D$ 1.4630.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 78.05; H, 12.51. Found: C, 77.85; H, 12.54.

The diketone gave a red color with alcoholic ferric chloride: when a solution of the diketone in a little methanol was shaken with warm aqueous cupric acetate, a blue oil separated. All attempts to crystallize this blue oil were unsuccessful.

When the enolate of acetone (19.1 g.) was prepared in liquid ammonia, essentially as described above, and brought into reaction with methyl apophytoate (49 g.) a product (59.7 g.) was obtained which, after distillation, had $n^{25}D$ 1.4500, and which consisted essentially of apophytoic acid, VIa.

Anal. Calcd. for $C_{19}H_{38}O_2$: C, 76.45; H, 12.83; neut. equiv., 298. Found: C, 76.82; H, 13.09; neut. equiv., 313.

2-(6′,10′,14′-Trimethyl-2′-pentadecyl)-4,6,7-trimethyl-5-hydroxycoumaron (VII).—A solution of the diketone VId (6.64 g.) in dry ethanol (10 cc.) was added to a solution of sodium (0.376 g.) in dry ethanol (50 cc.). The solution was stirred at room temperature for fifteen minutes, then was cooled to 15° and to it was slowly (one hour) added a solution trimethylquinone[25] (2.94 g.) in dry ethanol (30 cc.). The air in the flask was replaced by dry nitrogen and the flask was tightly stoppered and allowed to stand at room temperature for six and one-half days. The reaction mixture was poured onto ice, acidified with hydrochloric acid, and extracted three times with ether (100-cc. portions). The combined extracts were thoroughly washed with water and dried over sodium sulfate. The solvent was removed and the oil was subjected to distillation with steam; the distillate contained no organic material (*i. e.*, no IX, R = CH_3). The residue was taken up in ether, the solution was dried, the solvent was removed in a current of nitrogen. A red oil (1.76 g. unchanged VId) was removed from the product by distillation from a pot still under 0.001 mm. at a bath temperature of 130°. The residual oil from this distillation was stirred with petroleum ether (100 cc., b. p. 60–68°) and an insoluble black powder (1.12 g.) was removed. The solvent was removed in a current of nitrogen and the oil was distilled from a pot still under 0.001 mm. As the temperature of the bath was gradually raised, a dark oil (1.26 g.) distilled, followed by the coumaron VII (1.43 g., 21%) at 180°.

Anal. Calcd. for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.25; H, 11.08.

The absorption spectrum in the ultraviolet is shown in Fig. 1.

2-(6′,10′,14′-Trimethyl-2′-pentadecyl)-4,6,7-trimethyl-5-hydroxycoumaran (I).—The coumaron VII (100 mg.) in acetic acid (15 cc.) was subjected for four hours to the action of hydrogen at 68° under a pressure of 20 lb. and in the presence of palladium–charcoal catalyst (10%). The catalyst was removed by centrifugation and the solvent was removed under reduced pressure (5 mm.) at 70°. The residual light brown oil weighed 92 mg.

Anal. Calcd. for $C_{29}H_{50}O_2$: C, 80.87; H, 11.70. Found: C, 80.56; H, 11.76. The absorption spectrum in the ultraviolet is shown in Fig. 2.

Allophanate.—A stream of cyanic acid was passed for ten minutes through a solution of the coumaran I (90 mg.) in dry benzene (5 cc., thiophene-free). The solution was set aside in a refrigerator for six and one-half days. The solid was removed and washed with hot benzene; the filtrate and benzene washings were combined and the solvent was removed in a stream of nitrogen. The gummy residue was crystallized from methanol, when it weighed 45 mg. and melted at 160–174°. Recrystallized twice more from methanol, the substance melted at 176–180°.

Anal. Calcd. for $C_{31}H_{52}O_4N_2$: C, 72.05; H, 10.15. Found: C, 72.35; H, 10.37.

The absorption spectrum in the ultraviolet is shown in Fig. 2.

Pentadecanone-2.—This was prepared exactly as described above (for compound VIc) from magnesium (20.4 g.), methyl bromide, cadmium chloride (83.5 g.) and myristoyl chloride (104 g., b. p. 154–160° at 10 mm.). The product was distilled under 3 mm. pressure; the fraction (59.8 g., 63%) boiling at 122–135° solidified on cooling and then melted at 35–39°.[26] The semicarbazone melted at 124–125°.[27] Considerable residue remained after removal of the ketone; this was distilled from a pot still under 0.001 mm. at a bath temperature of 240°. The distillate, recrystallized from dry ethanol, gave 1.3 g. of dimyristoylmethane, melting at 62–63°.

Anal. Calcd. for $C_{29}H_{56}O_2$: C, 79.75; H, 12.92. Found: C, 79.49; H, 12.93.

The copper derivative, recrystallized from dry ethanol, melted at 101–102°.

Heptadecandione-2,4.—This was prepared as described above (for VId) from sodium (17.75 g.), liquid ammonia, pentadecanone-2 (58 g.), and ethyl acetate (55.5 g.). Cupric acetate dihydrate (50 g.) in water (500 cc.) was added to a solution of the crude product in warm methanol, the copper derivative was removed, washed with water, triturated with warm ethanol and the suspension was cooled and filtered. A small portion of the copper compound, crystallized from dry ethanol, was blue-gray and melted at 118–119°. The copper compound, suspended in petroleum ether (b. p. 40–70°), was shaken with dilute sulfuric acid until the solid disappeared. The organic layer was removed, washed thoroughly with water, and the solvent was removed by distillation. The residue (41.5 g., 60%) melted at 43–45°. The diketone gave a cherry-red color with alcoholic ferric chloride, and the enol content, determined by the method of Cooper and Barnes[28] was 98%. Condensation of methyl myristate (24.2 g.) in petroleum ether (200 cc., b. p. 100–140°) with acetone (2.9 g.) in the presence of sodium hydride (2.4 g.) gave only small amounts (5–8 g.) of the diketone, which was impure (m. p. 41–48°, enol content, 53%). The bulk of the condensation product was myristic acid.

3-(2′,5′-Dihydroxy-3′,4′,6′-trimethylphenyl)-heptadecandione-2,4 (VIII, R = CH_3; R′ = n-$C_{13}H_{27}$).—A solution of heptadecandione-2,4 (14.8 g.) in dry ethanol (50 cc.) was added, with stirring and some cooling (20°) to sodium methoxide (from sodium, 1.15 g.) in ethanol (50 cc.). Trimethylquinone (7.5 g.) in dry ethanol (25 cc.) was slowly (one and one-half hours) added to the cooled (15–20°) solution of the enolate. The solution was stirred for two hours at room temperature, then cooled (0°) and acidified with iced hydrochloric acid and extracted three times with ether. The combined extracts were washed with water, filtered, and the solvent was removed. The oily residue was dissolved in warm methanol and the solution, when cooled, deposited 9.5 g. of material melting at 40–70°. This material, recrystallized first from petroleum ether and then from methanol, weighed 3 g. (14%) and melted at 90–91°. The analytical sample, crystallized twice from petroleum ether and three times from methanol, melted at 95–96°.

Anal. Calcd. for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11. Found: C, 74.44; H, 10.23.

Heptadecandione-2,4 (6.3 g., m. p. 43–45°) was recovered by recrystallization from methanol of the residue obtained when all the mother liquors from the above purification were combined and evaporated.

(25) Smith, Opie, Wawzonek and Prichard, *J. Org. Chem.*, **4**, 138 (1939).

(26) Dreger, Keim, Miles, Shedlovsky and Ross, *Ind. Eng. Chem.*, **36**, 610 (1944), report the m. p. as 40.5°.

(27) (a) Baumgarten, *Ber.*, **76**, 213 (1943), reported the m. p. as 124–125°; (b) Pickard and Kenyon, *Proc. Chem. Soc.*, **27**, 312 (1911), reported 126.5°.

(28) Cooper and Barnes, *Ind. Eng. Chem., Anal. Ed.*, **10**, 379 (1938).

2-*n*-Tridecyl-4,6,7-trimethyl-5-hydroxycoumaron (IX, R = *n*-$C_{13}H_{27}$).—The diketone VIII (560 mg.) was warmed on the steam-bath for one hour with aqueous sodium hydroxide (1 *N*, 20 cc.) in an atmosphere of nitrogen. (When air was allowed to come into contact with the reaction mixture, the product was a red oil which could not be crystallized.) The cooled mixture was acidified with hydrochloric acid and then steam-distilled. From the distillate there was obtained 51 mg. (20%) of 2-methyl-4,6,7-trimethyl-5-hydroxycoumaron (IX, R = CH_3), m. p. and mixed m. p., 136–137°. The residual oil in the distillation flask solidified on cooling; it was removed and crystallized from methanol, when it weighed 260 mg. (54%) and melted at 101–102°. The analytical sample, crystallized from methanol, melted at 102–104°.

Anal. Calcd. for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68. Found: C, 80.41; H, 11.04.

The absorption spectrum in the ultraviolet is shown in Fig. 1. The diketone VIII (430 mg.) was recovered unchanged after 500 mg. of it was boiled with hydrochloric acid (10 cc.) and ethanol (2 cc.) for seven hours; likewise, action of hydrogen chloride in refluxing acetic acid (10 cc.) for one hour upon the diketone (500 mg.) did not bring about ring closure; the recovery of diketone was 275 mg.

2-*n*-Tridecyl-4,6,7-trimethyl-5-hydroxycoumaran (X, R = *n*-$C_{13}H_{27}$).—The coumaron IX (75 mg.) in acetic acid (10 cc.) was shaken with hydrogen at 46° and under a pressure of 20 lb. for four hours in the presence of a palladium–charcoal catalyst. The solvent was removed under reduced pressure at 40°; the residue was dissolved in methanol and the catalyst was removed by centrifugation. The solution, when concentrated and cooled, deposited a white solid melting at 93–94°. When mixed with the coumaran (m. p. 102–104°), the substance also melted at 93–94°.

Anal. Calcd. for $C_{24}H_{40}O_2$: C, 79.94; H, 11.18. Found: C, 79.76; H, 11.22.

The absorption spectrum in the ultraviolet is shown in Fig. 2. The coumaron IX (360 mg.) in dry ethanol (10 cc.) was heated on the steam-bath for fifteen minutes with Raney nickel catalyst. The catalyst was removed, fresh catalyst was added, and the mixture was subjected to the action of hydrogen for one hour at 125° and 1600 lb. The product weighed 230 mg. and melted at 101–103°. This material, subjected to the same conditions as before, but at 140°, gave a product which melted at 97–99°, alone or when mixed with known IX. The absorption spectrum in the ultraviolet indicated that no reduction had occurred.

Summary

1. The coumaran 2-(6′,10′,14′-trimethyl-2′-pentadecyl) - 4,6,7 - trimethyl - 5 - hydroxycoumaran, I, an isomer of α-tocopherol, II, has been synthesized. The coumaran has been characterized by its absorption spectrum, by conversion into an allophanate melting at 176–180° and by the absorption spectrum of the latter. Although I differs from II only in the size of the hetero ring, I has only about 5% as much vitamin E activity as II.

2. The synthesis of Smith and King, whereby 2-isopropyl-5-hydroxycoumaran and homologs are produced, has been modified in such a way that the more accessible unsymmetrical acetylacylmethanes may be used instead of the symmetrical diketones. When the R of the acyl group has a relatively high molecular weight, the coumaron with the higher alkyl group is formed exclusively or in preponderant amounts; if two coumarons are formed, the simple one may be removed from the reaction product by steam distillation. In this way, 2-*n*-tridecyl-4,6,7-trimethyl-5-hydroxycoumaron (IX) R = *n*-$C_{13}H_{27}$, has been prepared and separated from 2,4,6,7-tetramethyl-5-hydroxycoumaron (IX, R = CH_3), formed in the same reaction. The coumaron IX (R = *n*-$C_{13}H_{27}$) has been reduced to the corresponding coumaran X (R = *n*-$C_{13}H_{27}$).

3. The absorption spectra of a number of intermediates in the above syntheses have been determined.

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Preparation and Cyclization of Certain Insecticidally Active α-Acetyl-δ-keto Esters

BY HERMAN WACHS AND OSCAR F. HEDENBURG

The condensation of ethyl acetoacetate with hexyl 3,4-methylenedioxystyryl ketone[1] at room temperature yields a mixture having high insecticidal activity. When allowed to crystallize, 3-hexyl - 5 - (3,4 - methylenedioxyphenyl) - 2 - cyclohexene-1-one (III) is obtained, which has been found to have the same insecticidal activity as the original mixture or the remaining mother liquor. This mother liquor contains resinous material and approximately 50% of 3-hexyl-5-(3,4-methylenedioxyphenyl) - 6 - carbethoxy - 2 - cyclohexene - 1 - one (IV). Proceeding on the assumption that the resinous portion was of little activity, it appeared desirable to devise a method by which the above ester (IV) could be obtained as the main product. The present paper describes the procedure developed to accomplish this purpose. This procedure also made it possible to obtain esters other than ethyl esters and to compare their relative effectiveness. The work was expanded to include compounds containing the furfuryl group in the 3 position of the cyclohexenone ring.

It was assumed that a Michael addition[2] takes place intermediate to the formation of the cyclohexenone ring. Taking advantage of the fact that such addition reactions are reversible,[3] by employing a large excess of ethyl acetoacetate and by

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(2) Michael, *J. prakt. Chem.*, **35**, 351 (1887).

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